REMARKS

Of claims 1-68 which were contained in the original application, claims 5-9, 23-27 and 37-65 have been cancelled. Claims 1-4, 10-22, 28-36 and 66-68, which are drawn to a method of treating atherosclerosis in a mammal with lysosomal acid lipase, remain under consideration.

In addition to this response, Applicants have attached a second Declaration under 37 CFR 1.132 from David Hui, Ph.D. The Examiner is reminded of the duty to consider such evidence. An expert declaration alone may be sufficient to satisfy the Applicants' burden with regard to the Examiner's obviousness rejection and such evidence must be considered, In re Piasecki, 745 F.2d 1468, 1471, 223 USPQ 785, 787 (Fed. Cir. 1984), and may be sufficient to overcome a prima facie case of obviousness. Id. at 1472, 223 USPQ at 788, (quoting In re Surrey, 50 C.C.P.A. 1336, 319 F.2d 233, 235, 138 USA 67, 69 (CCPA 1963)). This second Declaration states that based the art, the results of Grabowski and Du are very surprising and one would not expect exogenous administration of LAL to reduce and/or eliminate atherosclerotic lesions. Accordingly, based upon the Declaration and the arguments set forth below, it is requested that the Examiner's obviousness rejections be withdrawn.

Rejections Under 35 U.S.C. §103(a)

The Examiner has maintained his rejection of claims 1-36 and 66-68 under 35 U.S.C §103(a) as being unpatentable over Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), Walters et al. (1994) and Escary et al. (1998) in view of Coates et al. (1986).

In repeating the §103(a) rejection in his final office action, the Examiner maintained that the combined teachings of Chan et al., Bond et al., Pomerantz et al., Walters (sic) et al., and Escary et al. (1998) all provide examples where increasing LAL activity, albeit by secondary agents, reduces atherosclerosis, and, Coates et al. established that deficiencies in LAL increased the risk of developing atherosclerosis, thereby suggesting that remedying such a deficiency could constitute an effective therapy for atherosclerosis. Therefore, given the limited to non-existent success of gene therapy methods to date, the Examiner argues it would have been obvious to a person of ordinary skill in the art to increase LAL levels by direct addition of the enzyme. Applicants respectfully traverse this rejection.

As an initial matter, even if one combines the teachings of the above-cited references, they would not arrive at the present invention. The art relied on by the Examiner utilizes cholesterol ester hydrolase (CEH). This enzyme is chemically different and distinct from the lysosomal acid lipase (LAL) of the present invention. These are two very different enzymes with different sequences and biochemical pathways (see the attached Power Point presentation of April 5, 2004). As such, one would not be motivated to substitute one enzyme for the other.

The Examiner has maintained that Chan et al., Bond et al., Pomerantz et al., Walters (sic) et al., and Escary et al (1998) provide examples where increasing LAL activity, albeit by secondary agents, reduces atherosclerosis. The fact is that the emphasis in the articles is not on lysosomal acid lipase, but rather on a different enzyme – cholesteryl ester hydrolase (CEH). As was discussed during the April 5, 2004 interview, LAL and CEH function by very different biochemical pathways. As such, the Applicants have reviewed each of the above-cited articles and a summary of findings is provided below.

Chan et al.:

Chan et al. state that atherosclerosis may result from decreases in prostacyclin formation in the blood vessel wall due to inhibition by high concentrations of lipid peroxides in the blood and that prostacyclin stimulates cholesterol ester hydrolase. Accordingly, Chan et al. maintain that prostacyclin and other related prostaglandins may be useful for the prevention of atherosclerosis since they are thought to stimulate production of CEH (cholesterol ester hydrolase) for mobilization of cholesterol. Relevant sections of this article include the following:

- "Prostacyclin stimulates cholesterol ester hydrolase, the enzyme that converts cholesterol ester to free cholesterol for mobilization out of the cells. PGE_2 inhibits acyl CoA cholesterol-O-acyltransferase (ACAT), the enzyme that catalyzes the re-esterification of free cholesterol." Page 341.

- "Therefore, prostacyclin, by stimulating CE hydrolase, and PGE_2, by inhibiting ACAT, together will effectively decrease intracellular cholesterol ester and cholesterol by means of enhancing cholesterol egress, resulting in possible regression of atherosclerosis." Page 350.

Thus, Chan et al. teaches that stimulation of cytoplasmic CE hydrolase (now known as hormone sensitive lipase) will require ACAT inhibition for possible regression of atherosclerosis. In contrast, he claims of the present application are narrowly directed to only to lysosomal acid lipase and this teaches away from the need for ACAT inhibition. Indeed, the article by Du et al. (2003) teaches that lysosomal acid lipase alone without inhibition of ACAT decreases atherosclerosis.

Serial No. 09775,517

Bond et al:

Bond et al. describe the use of calcium channel blockers (antagonists) for stimulation of cholesteryl ester hydrolase activity wherein these calcium channel blockers play a secondary role in reduction of atherosclerotic lesions in that they stimulate production of the polypeptide cholesteryl ester hydrolase, which in turn is thought to play a role in clearance of cholesterol.

This article provides no new data over the previous work, but mentions lysosomal cholesteryl ester hydrolase on page S88. Again, the emphasis of Bond et al. and the cited reference is smooth muscle cells and is based on the increased activity of an acid lipase in smooth muscle cells only.

Pomerantz et al.:

Pomerantz et al., describe the use of calcium channel blockers (antagonists) for stimulation of cholesteryl ester hydrolase activity wherein cholesteryl ester hydrolase is thought to increase clearance of accumulated cholesterol (see abstract).

Relevant sections of this article include the following:

- "These calcium channel blockers also increased lysosomal and cytoplasmic cholesteryl ester hydrolase activities, but did not alter ACAT activity." "Taken together, our data demonstrate that calcium channel blockers reduce cholesterol content in vascular tissue by stimulating LDL catabolism through process that is mediated by PGI_2 and cyclic AMP." Page 251.

- "Thus, it is conceivable that a potential mechanism by which calcium channel blockers have anti-atherosclerotic properties may be due to their

ability to influence the processes of cholesterol delivery, hydrolysis and esterification in smooth muscle cells." Page 253

- "In summary, our data are consistent with the hypothesis that calcium channel blockers can increase LDL receptor activity [4,8], and decrease cellular cholesterol content [5, 21]." Page 259

Thus, while Pomerantz is directed to targeting CEH in smooth muscle cells, the present invention is specifically directed to LAL in the lysosomes. Also, Escary et al (1999) teaches away from the above suggestions by Pomerantz et al. since the lesions are increased in the presence of increased cholesteryl ester hydrolase activity.

Walters et al.

Walters et al. also describes the use of calcium channel blockers (antagonists) for stimulation of cholesteryl ester hydrolase activity wherein cholesteryl ester hydrolase is thought to increase clearance of accumulated cholesterol.

Relevant sections of this article include the following:

- "The mechanisms that may contribute to this effect include stimulation of cholesteryl ester hydrolase activity in smooth muscle cells, amelioration of hypercholestolemic-induced endothelial dysfunction, or inhibition of smooth muscle cell proliferation and migration." Page 1309.

Thus, Walters et al. teaches to the potential effects of CEH in smooth muscle cells and the phenomenology of altered atherosclerosis and administration of calcium channel blockers. No information is provided to address the role of lysosomal acid lipase or macrophages in this process.

Escary et al. (1998)

As previously discussed with the Examiner during the April 5, 2004 interview, Escary et al. teaches directly to the involvement of macrophages in atherosclerosis and increased hormone sensitive lipase activity. Escary et al. shows that increased hormone sensitive lipase activity in macrophages increases atherosclerosis/foam cells in a mouse model. Escary et al. proposes a mechanism of increased re-esterification via ACAT of liberated cholesterol in the presence of increased hormone sensitive lipase activity. This directly teaches away from the proposed effects of the previous cited references that implicate cholesterol ester hydrolase activity as anti-atherogenic and supports the proposed mechanism of Chan et al. In view of Chan et al, Escary et al. teaches way from the use of lysosomal acid lipase administration for treatment of atherosclerosis, since liberated cholesterol from the lysosome is expected to participate in the same re-esterification process. Thus, in view of Chan et al and Escary et al., supplemental lysosomal acid lipase would be expected to be pro-atherogenic, whereas Du et al. (2003) demonstrates that this is incorrect.

Coates et al.

Finally, Coates et al. teach that low acid lipase activity may represent an independent risk factor for the development of premature atherosclerosis due to inherited deficiencies in this enzyme. Coates et al. does not teach that administration of LAL would alleviate such a deficiency, nor does Coates suggest or motivate one skilled in the art to administer LAL in order to treat such a deficiency. Coates merely suggests that there may be a *familial link* for low acid lipase activity due to an inherited allele which confers low enzyme activity. Coates et al. does not teach or suggest any

methods of treatment for low LAL but rather is focused on a genetic link to low LAL levels.

Accordingly, one would not look to Chan et al., Bond et al., Pomerantz et al., Walters (sic) et al., and Escary et al. (1998) in view of Coates to support the proposition that direct (exogenous) administration of LAL would be expected to successfully clear atherosclerotic lesions, since Chan et al., Bond et al., Pomerantz et al., Walters (sic) et al., and Escary et al. (1998) are directed only to indirect production of CEH and Coates et al. discusses familial links to low LAL levels but does not teach or suggest any methods of remedying the problem.

In addition, the second attached declaration of Dr. David Hui states that the results of Grabowski and Du are unexpected and surprising in light of the current art and dogma in this area of research, which is primarily directed to the CEH pathway (see Power Point presentation of April 5, 2004). Accordingly, one would not be motivated to administer an exogenous LAL in order to treat atherosclerotic lesions.

In summary, none of these references, taken together, teach or suggest the present invention and the Examiner's rejections under 35 U.S.C. §103(a) have been overcome and should be withdrawn. Accordingly, the present application is in form for allowance and early reconsidcration and allowance of the claims, as currently pending, is earnestly solicited.

Respectfully submitted,

GREGORY GRABOWSKI

HONG DU

By Karlyn A. Schnapp

Karlyn A. Schnapp
Registration No. 45,558
Attorney for Applicants

FROST BROWN TODD LLC
2200 PNC Center
201 East Fifth Street
Cincinnati, Ohio 45202
(513) 651-6865

Serial No. 09775,517

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below:

Karen S. Kruetzkamp
(Type or print name of person signing certification)

Karen S. Kruetzkamp
Signature

4-19-04
Date

FAX Telephone No.: (703) 872-9306

Attn: Examiner Weber

Art Unit No.: 1651

Serial No. 09/775,517

CinLibrary/1389335.1